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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/165,546	10/02/98	ALEXANDER K	LUD5466.4-JE

EXAMINER	
DIBRINO, M	
ART UNIT	PAPER NUMBER
1644	19

DATE MAILED: 05/22/01

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HM12/0522

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/165,546	Alexander et al.
Examiner	**Art Unit**
Marianne DiBrino	1644

– The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on Apr. 13, 2001, Apr. 11, 2000, Jan 23, 2001 & Apr. 19, 1999

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) 1-73 is/are pending in the applica

4a) Of the above, claim(s) 6-8, 11-13, 16-54, and 61-73 is/are withdrawn from considera

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) 1-5, 9, 10, 14, 15, and 55-60 is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirem

Application Papers

9) ☒ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 6&18 filed 7/2/98 & 4/19/99

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

DETAILED ACTION

1. Applicant's amendment filed 4/19/01 and Applicant's responses filed 4/11/00 and 1/23/01 are acknowledged and have been entered.

Claims 1-73 are pending.

2. Applicant's election of Group I (claims 1-5, 9, 10, 14, 15 and 55-60), and species of SEQ ID NO: 10 in the amendment filed 4/19/01 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1-5, 9, 10, 14, 15 and 57, 59 and 60 read on the elected species, SEQ ID NO: 10. Upon consideration of the prior art, the search has been extended to include SEQ ID NO: 8, 9, 11, 12, 13 and 7, and claims 55, 56 and 58 have been rejoined to the elected claims. Claim 60 is being examined where the at least one other peptide is SEQ ID NO: 8, 9 or 10.

Accordingly, claims 6-8, 11-13, 16- 54, 61-73 (non-elected groups II-XVIII) are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to non-elected inventions.

Claims 1-5, 9, 10, 14, 15 and 55-60 are currently being examined.

With regard to Applicant's request on page 2 of the response filed 1/23/01 for reference to the prior restriction requirement, the following applies: Since 37 CFR 1.142(a) provides that restriction is proper at any stage of prosecution up to final action, a second requirement may be made when it becomes proper, even though there was a prior requirement with which applicant complied. Ex parte Benke, 1904 C.D. 63, 108 O.G. 1588 (Comm'r Pat. 1904). Proper restriction of the instant pending claims was made in the second restriction requirement mailed 1/04/01 for the reasons enunciated in items 3-35 of the said restriction requirement.

3. The petition under 37 C.F.R. 1.48(a) filed 11/20/00 to add inventor Jan W. Drijfthout is hereby DENIED. The written consent of assignee Academisch Ziekenhuis Leiden to whom Inventor Drijfhout made assignment is missing. In addition, the following assignment documents appear to be missing: for Memorial Sloan-Kettering Cancer Center, the assignment made by Inventors Ritter and Scanlan; for Ludwig Institute for Cancer Research, the assignment made by Inventor Gure; in addition, Inventors Ritter and Scanlon for whom an assignment to Ludwig Institute for Cancer Research are not listed in the consent of the assignee.

4. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because: the filing date of parent application serial no. 09/062,422 is incorrect. The declaration lists the filing date as 4/12/98, whereas the filing date appears to be 4/17/98. In addition, declaration does not list the date that the instant application was filed on, nor the serial number.

5. Applicants are required under 37 C.F.R. 1.821(d) to amend the specification to list the appropriate SEQ ID NOS for sequences disclosed in the specification (for example, the Brief Description of the Drawings for Figure 3). In addition, it is noted that Applicant has disclosed on page 25 at lines 12-14, "In the Table which follows, the amino acid sequence...and the positions of SEQ ID NO: 1 are given. It it requested that Applicant amend the said Table at line 1 on page 26 to disclose "amino acid residues of SEQ ID NO: 1", or some indicator in the said Table that the positions represent amino acid residues of SEQ ID NO: 1.

6. The references crossed out in the Form 1449 filed 7/2/99 have been considered in the Form 1449 filed 4/19/99.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Applicant is reminded of the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 64, No. 244, pages 71427-71440, Tuesday December 21, 1999; the following rejection is set forth herein.

Claims 1, 3, 9 and 57-59 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The specification does not provide adequate written description of the claimed invention. The legal standard for sufficiency of a patent's (or a specification's) written description is whether that description "reasonably conveys to the artisan that the inventor had possession at that time of the. . .claimed subject matter", Vas-Cath, Inc. V. Mahurkar, 19 USPQ2d 1111 (Fed. Cir. 1991). In the instant case, the specification does not convey to the artisan that the applicant had possession at the time of invention of: (1) the claimed isolated polypeptide, and composition thereof, which binds to MHC-class II HLA-DR53 and which comprises at least 18 and no more than 25 amino acids, having at least one binding motif, wherein the first amino acid of the motif is Tyr, Phe, Trp or Leu and the fourth amino acid is Ala or Ser; (2) a

composition comprising SEQ ID NO: 7 and at least one other peptide, the amino acid sequence of which is found in the protein encoded hy SEQ ID NO: 1 and which complexes with a class l MHC or class II MHC molecule.

There is insufficient disclosure in the specification on such a polypeptide or composition.

To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli , 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "hy describing the invention, with all its claimed limitations, not that which makes it obvious," and hy using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood , 107 F.3d at 1572, 41 USPQ2d at 1966.

An adequate written description of a polypeptide "requires a precise definition, such as hy structure...," not a mere wish or plan for ohtaining the claimed chemical invention. Fiers v. Revel , 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description ... requires more than a mere statement that it is part of the invention; Id. at I170, 25 USPQ2d at I606.

The specification does not disclose the structure of said isolated polypeptide, except for two motif amino acid residues. The specification does not disclose an isolated polypeptide that is longer than 18 amino acid residues, has the said motif amino acid residues, and that binds to HLA-DR53. The specification does not disclose the structure of the suhsequences of SEQ ID NO: 1 which can be the "at least one other peptide" of the composition of claim 57 that hind to class I MHC or class II MHC molecules.

The specification discloses six polypeptides with the required motif amino acid residues (SEQ ID NO: 8-13) which hind to HLA-DR53 and that at least three of these polypeptides (SEQ IDNO: 8-10) sensitize CD4+ T cells to release IFN-γ (especially page 29 at lines 25-26 and page 30 at lines 1-I4). All of these polypeptides are 18-mers. The specification discloses SEQ ID NO: 4, 5, 6, 8, 9 and 10, that SEQ ID NO: 4, 5 and 6 hind to the class I molecule HLA-A2 and are recognized hy CTL (page 27 at lines 19-21 and page 25, lines 25-27).

In claims involving chemical materials, generic formulae usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass. Accordingly, such a formula is normally an adequate description of the claimed genus. However, a generic statement such as "hinds to MHC-Class ll HLA-DR53 molecules", "comprises at least 18 and no more than 25 amino acids" and which has at least one HLA-DR53 hinding motif recited in

instant claim 1, or a composition comprising "at least one other peptide" the amino acid sequence of which is found in a protein of defined sequence, and which binds to a MHC class I or class II molecule, or a composition comprising "at least one other peptide" the amino acid sequence of which is found in a protein of defined sequence, and which binds to a MHC class I or class II molecule, without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by the property of being able to bind to HLA-DR53 in the case of the isolated peptide, or except by the property of being able to bind any one of the hundreds of MHC class 1 or class II molecules in the case of the "at least one other peptide" of the composition. It does not specifically define any of the polypeptides that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others, other than two motif amino acid residues in the case of the isolated polypeptide. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by the property of comprising "at least 18 and no more than 25 amino acids" and binding to HLA-DR53, nor "at least one other peptide" which binds to class I or class II MHC, does not suffice to define the genus because it is only an indication of what the property the polypeptide or the peptide has. See Fiers, 984 F.2d at 1169-71, 25 USPQ2d at 1605-06. It is only a definition of a useful result rather than a definition of what achieves that result. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin [e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material.

The instant disclosure of a few peptides that are 18-mers which bind to HLA-DR53 and three of which stimulate CD4+ cells, and of three peptides that bind to HLA-A2 and stimulate CTL, does not adequately describe the scope of the claimed invention, which encompasses a substantial variety of subgenera. Since the disclosure fails to provide sufficient relevant identifying characteristics that identify members of the genus, and given the broad genus claimed, the disclosure of a few peptides of defined sequence is insufficient to describe the claimed genus.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 1-5, 9-10, 14-15 and 55-60 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claim 1 is indefinite in the recitation of "at lease one". It is suggested that Applicant amend said phrase to recite "at least one".

b. Claims 1-5, 9, 10 and 14 are indefinite in the recitation of "polypeptide" and claims 57 and 60 are indefinite in the recitation of "peptide" because it is not clear if the peptides defined by SEQ ID NO: 8-10 recited in the instant claim 60 which are the same SEQ ID NO: 8-10 recited in claims 4, 5, 10 and 14 as "polypeptides" are "peptides" or "polypeptides".

11. With regard to application of prior art, SEQ ID NO: 7 instant application is not entitled to priority of the parent application 08/725,182 because the peptide consisting of SEQ ID NO: 7 is not disclosed in the said parent application.

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 55-58 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Lethe et al (U.S. Patent No. 5,811,519) in view of Rammensee et al (Immunogenetics 41: 178, 1995).

Lethe et al disclose the amino acid sequence encoded by SEQ ID NO: 1 of the instant application (especially columns 35-38, both SEQ ID NO: 6, bottom line showing amino acid sequence, and SEQ ID NO: 7 (the amino acid sequence) of Lethe et al) and fragments of said amino acid sequence. Lethe et al disclose a protein, LL-1 that is a tumor rejection antigen precursor (TRAP) (SEQ ID NO: 7 of Lethe et al and column 14, lines 31-36 and 55-57). Lethe et al also disclose PBL loaded with synthetic peptides derived from the sequence of the LL-1 protein, said peptide sequences generated by matching the consensus motif for the appropriate HLA class I molecule to localize the antigenic peptide within (especially column 30, lines 12-22), i.e., Lethe et al disclose a method for determining the antigenic peptide(s) within the LL-1 protein by identifying amino acid residues within the LL-1 protein which correspond to the HLA-binding motif. Lethe et al further disclose a fragment of LL-1 between 5 and 209 amino acid residues in length (claim 2) which binds a polypeptide binding agent (claim 7). Polypeptide binding agents encompass HLA molecules. Lethe also discloses that the skilled artisan can determine which HLA molecule binds to tumor rejection antigens (TRAs) from LL-1 (tumor rejection antigens, especially column 14, lines 55 and continuing through column 15, line 20). Lethe et al disclose that expression of TRAPS or tumor specific

genes such as LL-1 can provoke an immune response against the tumor cells (especially column 1, lines 19-24 and lines 54-60). Lethe et al disclose that TRAPS may be used to generate therapeutics for enhancement of the immune system response to tumors expressing such genes and proteins (especially column 1, lines 54-60). Lethe et al also disclose that fragments of LL-1 which correspond to TRAs, i.e., one or more than one peptide, may be combined with materials such as adjuvants to produce vaccines useful in treating disorders characterized by expression of the tumor antigen (especially column 19, lines 25-33, and column 20, lines 51-60).

Lethe et al do not teach an isolated peptide consisting of the amino acid sequence set forth in SEQ ID NO: 7 (LLMWITQCFL) of the instant application, nor a composition comprising the said peptide and an adjuvant, or comprising the said peptide and at least one other peptide, the amino acid sequence of which is found in the protein encoded by SEQ ID NO: 1.

Rammensee et al teach the HLA-A2 binding motif which is Leu (L) or Met (M) at position 2 and Leu (L) or Val (V) at the carboxy terminal position (especially Table 2, "Anchor or auxiliary anchor residues"). Rammensee teaches peptides of 9, 10 and 11 amino acid residues in length which bind to HLA-A2 (especially page 193, Table 2).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have identified the HLA-A2 binding peptides from a TRAP such as the LL-1 of Lethe et al using the HLA-A2 binding motif of Rammensee et al to obtain the peptide having the sequence LLMWITQCFL (SEQ ID NO: 7 of the instant application, or amino acid residues 158-167 of SEQ ID NO: 1 of the instant application and also of SEQ ID NO: 6 of Lethe et al). LLMWITQCFL is a 10-mer peptide. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made an immunogenic composition comprising said isolated peptide and a pharmaceutically acceptable adjuvant as taught by Lethe et al and to use more than one peptide in a composition as taught by Lethe et al.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this because Lethe et al teach the sequence of SEQ ID NO: 6 is a TRAP from which TRAs may be identified using consensus HLA binding motifs, such as the HLA-A2 binding motif of Rammensee et al, for the purpose of generating immunotherapeutics for enhancement of the immune system response to tumor antigens.

14. SEQ ID NO: 8, 9, 10, 11, 12 and 13 appear to be free of the prior art.

15. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware of in the specification.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marianne DiBrino whose telephone number is (703) 308-0061. The examiner can normally be reached Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

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